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ning of each regular issue of the PCT Gazette.*

(54) Title: METHOD OF TREATING RHEUMATOID ARTHRITIS BY INTERFERING WITH EXPRESSION OF DC-SIGN BY  
MACROPHAGES AND DIAGNOSIS THEREOF

(57) Abstract: The C-type lectin DC-SIGN is absent in normal synovium but is highly expressed by CD68 positive macrophages in the synovium of rheumatoid arthritis patients. Accordingly, rheumatoid arthritis is diagnosed or treated by, respectively, assaying or blocking DC-SIGN. This can be accomplished by the use of agents, e.g., antibodies, which bind specifically to DCSIGN. Agents that bind to ICAM-3 are used to block inhibition of activation of macrophages by DC-SIGN-ICAM-3 interaction and cause inhibition of rheumatoid arthritis symptoms.

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## INTERNATIONAL SEARCH REPORT

National Application No

PCT/IB 03/05181

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/70 G01N33/564 C12N5/00 A61P19/02 A61K31/7004

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, SCISEARCH, BIOSIS, MEDLINE, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | EP 1 046 651 A (KONINKL UNIVERSITEIT NIJMEGEN) 25 October 2000 (2000-10-25)<br>paragraphs [0009], [0010], [0014]<br>paragraph [0097]<br>paragraphs [0035], [0036], [0043]<br>paragraphs [0083], [0087]<br>-----                                      | 1-3                   |
| X          | WO 92/22323 A (BLOOD RES CENTER)<br>23 December 1992 (1992-12-23)<br>page 2, paragraph 7 - page 3, paragraph 1<br>page 15, paragraph 2 - paragraph 3<br>page 45, line 6<br>page 54, paragraph 3 - paragraph 4<br>claims 1-5,10,11,18<br>-----<br>-/- | 1-3                   |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | WO 02/14366 A (GROOT PIETER CORNELIS ;OOSTERHOUT ANTOON J M VAN (NL); UNIV UTRECH) 21 February 2002 (2002-02-21)<br>page 3, line 22 - line 37<br>page 14, line 18<br>page 58, paragraph 2<br>page 59, line 36 - page 60, line 29<br>-----   | 1,2                   |
| X          | WO 00/63251 A (UNIV NIJMEGEN ;TORENSMA RUURD (NL); FIGDOR CARL GUSTAV (NL); GEIJT) 26 October 2000 (2000-10-26)<br>claims 1-3,10<br>page 7, paragraph 4<br>-----  | 1-3                   |
| P,A        | VAN LENT P L E M ET AL: "Expression of the dendritic cell-associated C-type lectin DC-SIGN by inflammatory matrix metalloproteinase-producing macrophages in rheumatoid arthritis synovium and interaction with intercellular adhesion molecule 3-positive T cells"<br>ARTHRITIS AND RHEUMATISM 01 FEB 2003<br>UNITED STATES,<br>vol. 48, no. 2,<br>1 February 2003 (2003-02-01), pages<br>360-369, XP008028520<br>ISSN: 0004-3591<br>page 368, column 2, paragraph 2 -<br>paragraph 3<br>----- |                       |
| A          | VARSANI H ET AL: "Synovial dendritic cells in juvenile idiopathic arthritis (JIA) express receptors activator of NF-[kappa]B (RANK)"<br>RHEUMATOLOGY 01 APR 2003 UNITED KINGDOM,<br>vol. 42, no. 4, 1 April 2003 (2003-04-01),<br>pages 583-590, XP008028518<br>ISSN: 1462-0324<br>page 583, column 1 - column 2<br>-----   |                       |
| A          | EL-GABALAWY HANI ET AL: "Expression of ICAM-R (ICAM-3), a novel counter-receptor for LFA-1 in rheumatoid and nonrheumatoid synovium: Comparison with other adhesion molecules"<br>ARTHRITIS AND RHEUMATISM,<br>vol. 37, no. 6, 1994, pages 846-854,<br>XP008028525<br>ISSN: 0004-3591<br>abstract<br>page 847, column 1, paragraph 3<br>-----   |                       |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 03/05181

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-2 (partially), 3

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 14-18 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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## Continuation of Box I.2

Claims Nos.: -

Claim 1 encompasses a genus of compounds defined only by their function (blockers of interaction between DC-SIGN and ICAM-3), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application, namely mannan and D-mannose) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, no search has been performed for claim 1 (Art. 5 and Art. 6 PCT).

Present claim 2 relates to an extremely large number of possible compounds, namely mannose carbohydrates. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claim 3, mannan and mannose.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-2 (partially); 3

Use of the mannose carbohydrates mannan or D-mannose for treating rheumatoid arthritis.

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2. claims: 1-2 (partially); 4

Use of the fucose carbohydrate L-fucose for treating rheumatoid arthritis.

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3. claims: 1-2 (partially); 5

Use of the plant lectin concanavalin A for treating rheumatoid arthritis.

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4. claims: 1-2 (partially); 6

Use of the antibiotic pradimicin A for treating rheumatoid arthritis.

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5. claims: 1-2 (partially); 7

Use of the sugars N-acetyl-D-glucosamine or galactose for treating rheumatoid arthritis.

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6. claims: 1-2 (partially); 8

Use of the proteins glycoprotein gp120, or a fragment thereof for treating rheumatoid arthritis.

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7. claims: 1-2 (partially); 9-12

Use of the antibodies AZN-D1, AZN-D2 for treating rheumatoid arthritis.

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8. claims: 1-2 (partially); 13

Use of soluble DC-SIGN, or a fragment of DC-SIGN that bind ICAM-3 for treating rheumatoid arthritis.

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9. claims: 14-18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method to diagnose if a human has rheumatoid arthritis by measuring the percentage of inflammatory cells that express DC-SIGN from synovia of said humans.

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10. claims: 19-25

Method to isolate macrophages from other cells in a biological sampks, contacting said sample with an agent binding DC-SIGN and separating cells that bind to that agent from cells that do not bind to said agent.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/05181

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---|---------------------|----------------------------|---------------------|
| EP 1046651                                | A | 25-10-2000          | EP 1046651 A1              | 25-10-2000          |
|   |   |                     | AU 4152600 A               | 02-11-2000          |
|   |   |                     | CA 2330231 A1              | 26-10-2000          |
|   |   |                     | EP 1086137 A1              | 28-03-2001          |
|   |   |                     | JP 2003502283 T            | 21-01-2003          |
|   |   |                     | WO 0063251 A1              | 26-10-2000          |
|   |   |                     | NZ 508723 A                | 19-12-2003          |
| -----                                     |   |                     |                            |                     |
| WO 9222323                                | A | 23-12-1992          | AU 670243 B2               | 11-07-1996          |
|   |   |                     | AU 2237692 A               | 12-01-1993          |
|   |   |                     | BG 61682 B1                | 31-03-1998          |
|   |   |                     | BG 98287 A                 | 15-08-1994          |
|   |   |                     | BR 9206142 A               | 27-12-1994          |
|   |   |                     | CA 2110387 A1              | 23-12-1992          |
|   |   |                     | CN 1069522 A               | 03-03-1993          |
|   |   |                     | CZ 9302702 A3              | 17-08-1994          |
|   |   |                     | EP 0590051 A1              | 06-04-1994          |
|   |   |                     | FI 935500 A                | 09-02-1994          |
|   |   |                     | HU 66617 A2                | 28-12-1994          |
|   |   |                     | IE 921893 A1               | 16-12-1992          |
|   |   |                     | IL 102176 A                | 13-09-2001          |
|   |   |                     | JP 3288042 B2              | 04-06-2002          |
|   |   |                     | JP 6509706 T               | 02-11-1994          |
|   |   |                     | MX 9202804 A1              | 01-12-1992          |
|   |   |                     | NO 934491 A                | 11-02-1994          |
|   |   |                     | NZ 243114 A                | 28-03-1995          |
|   |   |                     | RO 115415 B                | 28-02-2000          |
|   |   |                     | RU 2130782 C1              | 27-05-1999          |
|   |   |                     | SK 139593 A3               | 05-10-1994          |
|   |   |                     | WO 9222323 A1              | 23-12-1992          |
|   |   |                     | US 5629162 A               | 13-05-1997          |
|   |   |                     | US 5891841 A               | 06-04-1999          |
|   |   |                     | ZA 9204276 A               | 31-03-1993          |
| -----                                     |   |                     |                            |                     |
| WO 0214366                                | A | 21-02-2002          | EP 1182255 A1              | 27-02-2002          |
|   |   |                     | AU 9435701 A               | 25-02-2002          |
|   |   |                     | CA 2419725 A1              | 21-02-2002          |
|   |   |                     | EP 1309689 A2              | 14-05-2003          |
|   |   |                     | WO 0214366 A2              | 21-02-2002          |
|   |   |                     | US 2003232037 A1           | 18-12-2003          |
| -----                                     |   |                     |                            |                     |
| WO 0063251                                | A | 26-10-2000          | EP 1046651 A1              | 25-10-2000          |
|   |   |                     | AU 4152600 A               | 02-11-2000          |
|   |   |                     | CA 2330231 A1              | 26-10-2000          |
|   |   |                     | EP 1086137 A1              | 28-03-2001          |
|   |   |                     | JP 2003502283 T            | 21-01-2003          |
|   |   |                     | WO 0063251 A1              | 26-10-2000          |
|   |   |                     | NZ 508723 A                | 19-12-2003          |
| -----                                     |   |                     |                            |                     |